


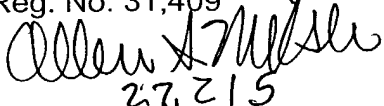
|   |  |  |
|---|--|--|
| <b>TRANSMITTAL LETTER TO THE UNITED STATES<br/>DESIGNATED / ELECTED OFFICE (DO/EO/US)<br/>CONCERNING A FILING UNDER 35 U.S.C. 371</b> |  | ATTORNEY'S DOCKET NUMBER<br><b>P67431US0</b>                       |
|   |  | US APPLICATION NO. (if known, use 35 CFR 1.51)<br><b>09/926820</b> |
| INTERNATIONAL APPLICATION NO.<br><b>PCT/EP99/04331</b>  | INTERNATIONAL FILING DATE<br><b>22 June 1999</b> | PRIORITY DATE CLAIMED<br><b>22 June 1999</b>                       |
| TITLE OF INVENTION<br><b>SERINE PROTEASE INHIBITORS</b>   |  |  |
| APPLICANT(S) FOR DO/EO/US<br><b>Wolf-Georg FORSSMANN, Hans-Juergen MAEGERT, Ludger STAENDKER and Peter KREUTZMANN</b>                 |  |  |

**Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.**

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11. to 16. below concern other document(s) or information included:**

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.  
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
  - International Search Report - EPO
  - PCT/IB/301 Form
  - PCT/IB/308 Form
  - First Page of Publication
  - International Preliminary Examination Report - with no annexes
  - Sequence Listing

|  |                     |   |             |  |              |
|--|---------------------|---|-------------|--|--------------|
| US APPLICATION NO (If known, see 37 CFR 1.51)<br><b>097926820</b>  |                     | INTERNATIONAL APPLICATION NO<br><b>PCT/EP99/04331</b> |             | ATTORNEY'S DOCKET NUMBER<br><b>P67431US0</b> |              |
| 17. <input checked="" type="checkbox"/> The following fees are submitted:<br><b>Basic National Fee (37 CFR 1.492(a)(1)-(5)):</b><br>Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) ... \$710.00<br>No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ... \$740.00<br>Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) ..... <b>\$1040.00</b><br>International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... \$100.00<br>Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) ..... <b>\$890.00</b><br><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b> |                     |   |             | CALCULATIONS                                 | PTO USE ONLY |
|  |                     |   |             | \$ 890.00                                    |              |
| Surcharge of \$130.00 for furnishing the <b>oath or declaration</b> later than<br><input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).   |                     |   |             | \$ 130.00                                    |              |
| <b>Claims</b>  | <b>Number Filed</b> | <b>Number Extra</b>                                   | <b>Rate</b> |  |              |
| Total Claims   | 14 - 20 =           | -0-   | x \$18.00   | \$   |              |
| Independent Claims   | 1 - 3 =             | -0-   | x \$84.00   | \$   |              |
| Multiple Dependent Claim(s) (if applicable)  |                     |   | + \$280.00  | \$   |              |
| <b>TOTAL OF ABOVE CALCULATIONS =</b>   |                     |   |             | \$ 1020.00                                   |              |
| Reduction by 1/2 for filing by <b>small entity</b> , if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).   |                     |   |             | \$ 510.00                                    |              |
| <b>SUBTOTAL =</b>  |                     |   |             | \$ 510.00                                    |              |
| Processing fee of \$130 for furnishing the <b>English translation</b> later than<br><input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f))   |                     |   |             | \$   |              |
| <b>TOTAL NATIONAL FEE =</b>  |                     |   |             | \$ 510.00                                    |              |
| Fee of \$40.00 for recording the enclosed <b>assignment</b> (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).   |                     |   |             | \$   |              |
| <b>TOTAL FEES ENCLOSED =</b>   |                     |   |             | \$ 510.00                                    |              |
|  |                     |   |             | Amt. to be refunded:                         | \$           |
|  |                     |   |             | Amt. charged:                                | \$           |
| a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>510.00</u> to cover the above fees is enclosed.<br>b. <input type="checkbox"/> Please charge my Deposit Account No. <b>06-1358</b> in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.<br>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. <b>06-1358</b> . A duplicate copy of this sheet is enclosed.  |                     |   |             |  |              |
| SEND ALL CORRESPONDENCE TO:<br><b>JACOBSON HOLMAN PLLC</b><br>400 7th Street, N.W., Suite 600<br>Washington, DC 20004<br>202-638-6666<br><b>CUSTOMER NUMBER: 00136</b>   |                     |   |             |  |              |
| By <br>William E. Player<br>Reg. No. 31,409<br><br>27,215   |                     |   |             |  |              |

09/926820, 05/06/02  
Rec'd PCT/PTO 06 MAY 2002  
09/926820

ATTY. DOCKET NO. P67431US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: FORSSMANN et al.

Serial No.: 09/926,820

Filed: December 26, 2001

For: SERINE PROTEASE INHIBITORS

**AMENDMENT**

Commissioner of Patents

**BOX PCT**

Washington, D.C. 20231

Sir:

The instant amendment is submitted in conjunction with the Response to Notice to Comply With Sequence Rules, submitted herewith.

IN THE SPECIFICATION

Replace the originally filed Sequence Listing with the Sequence Listing filed concurrently herewith.

REMARKS

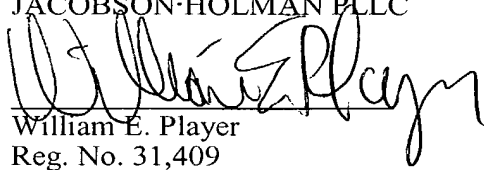
By the instant amendment, the Sequence Listing filed, concurrently herewith, is added to the specification.

Favorable action is requested.

Respectfully submitted,

JACOBSON-HOLMAN PLLC

By:

  
William E. Player  
Reg. No. 31,409

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Atty. Dkt. No.: P67431US0  
Date: May 6, 2002  
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09/926820

531 Rec'd PCT 26 DEC 2001

Atty. Dkt. No. P67431US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Wolf-Georg Forssmann

Serial No.: National Stage of PCT/EP99/04331

Filed: HEREWITH

For: SERINE PROTEASE INHIBITORS

**PRELIMINARY AMENDMENT**

Commissioner of Patents  
Washington, D.C. 20231

Sir:

Prior to calculating the filing fee, please amend the captioned application as follows.

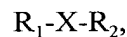
IN THE CLAIMS

Cancel claims 1-14, without prejudice or disclaimer.

Add the following claims.

15. A serine protease inhibitor having the amino acid sequence according to SEQ ID NO: 1.

16. A fragment of the serine protease inhibitor having the amino acid sequence



wherein  $R_1$  is  $NH_2$ , an amino acid or a peptide with up to 100 amino acids, and  $R_2$  is  $COOH$ ,  $CONH_2$ , an amino acid or a peptide with up to 100 amino acids, and X is selected from SEQ ID NOS: 2 to 6.

17. A nucleic acid coding for a serine protease inhibitor according to claim 15, especially SEQ ID NOS: 7 to 12.

PCT/EP99/04331  
Atty. Dkt. No. P67431US0

18. A medicament containing at least one serine protease inhibitor according to claim 15 and/or a nucleic acid coding for the serine protease inhibitor, optionally together with a pharmaceutical vehicle.
19. The medicament according to claim 18, containing from 0.01 to 1000 mg per kg of body weight of the serine protease inhibitor and/or the nucleic acid.
20. Use of the serine protease inhibitor according to claim 15 for preparing a medicament for the treatment of acute or chronic cervix inflammations, inflammations of Bartholin's glands and other vaginal regions, tonsillitis, pharyngitis and laryngitis, acute or chronic inflammatory processes accompanied by excessive formation of mucus and the resulting acute emergency situations, postoperative bleedings due to hyperfibrinolysis, and for the prophylaxis of lung emphysema formation in deficiencies of  $\alpha_1$ -proteinase inhibitor.
21. Use of the medicament according to claim 18 for the therapy of asthma, AIDS, pneumonia, tumor diseases and leukemia.
22. Use of the nucleic acid according to claim 17 for preparing a medicament for use in gene therapy for the curing and prophylaxis of acute or chronic cervix inflammations, inflammations of Bartholin's glands and other vaginal regions, tonsillitis, pharyngitis and laryngitis, acute or chronic inflammatory processes accompanied by excessive formation of mucus and the resulting acute emergency situations, postoperative bleedings due to hyperfibrinolysis, and for the prophylaxis of lung emphysema formation in deficiencies of  $\alpha_1$ -proteinase inhibitor.

23. Antibodies or antibody fragments against epitopes of the compound according to claim 15.
24. Poly- or oligonucleotides which will hybridize to regions of the cDNA or corresponding RNA under stringent conditions and optionally prevent the expression of coding regions of the genes coding for the compound according to claim 15.
25. A diagnostic agent containing at least one compound according to claim 23.
26. A medicament containing at least one compound according to claim 23 in a therapeutically effective amount.
27. Use of the compound of claim 23 for preparing a medicament for the treatment of diseases involving too high an expression of the serine protease inhibitor or too high an activity of the regions coding for the serine protease inhibitor.
28. DNA coding for the compound of claim 15 and/or RNA involved in the transcription or translation of the compound.

The present claims are 15-28.

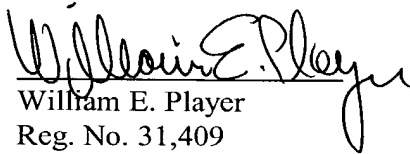
The present claims correspond to original claims 1-14, rewritten to eliminate multiple dependencies and to more clearly define the invention.

PCT/EP99/04331  
Atty. Dkt. No. P67431US0

Favorable action is requested.

Respectfully submitted,

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4/PRTS

531 Rec'd PCT.

26 DEC 2001

SMB

Serine Protease Inhibitors

The present invention relates to serine protease inhibitors, cDNA coding for serine protease inhibitors, medicaments containing such inhibitors or their coding nucleic acid, use of the compounds according to the invention for the preparation of medicaments for the treatment of various indications, antibodies or antibody fragments against epitopes of the compounds according to the invention, poly- or oligonucleotides which will hybridize to genes of the compounds according to the invention, a diagnostic agent for detecting the compounds according to the invention, and medicaments containing antibodies or poly- or oligonucleotides according to the invention.

Proteolytic processes play an important physiological role in all organisms; a distinction has to be made between non-specific and specific proteolytic reactions. The former include, for example, the digestion of food in the digestive tract by endopeptidases, and the intracellular degradation of used endogenous substances and phagocytosed materials by lysosomal proteases. Specific proteolyses mostly serve for the conversion of a proenzyme to its active form, as in the conversion of trypsinogen to trypsin, and of chymotrypsinogen to chymotrypsin, and in the callicrein-kinin cascades and the blood clotting cascade. Depending on the structure of the reactive site of the proteinases involved, they are classified into the classes of serine proteases (e.g., chymotrypsin, trypsin, elastase and cathepsin G), aspartate proteases (e.g., cathepsin D, cathepsin E and pepsin), cysteine proteases (e.g., cathepsin B, cathepsin H and cathepsin L), and the metallo-proteases (e.g., collagenase and thermolysin).

In order to be able to correct the proteolytic processes which often proceed in a cascade, the organisms is provided with a number of other proteins, the protease inhibitors (for a survey, see Laskowski and Kato, 1980, and Bode and



Huber, 1992). Thus, the liver-synthesized human plasma protease inhibitors  $\alpha_1$ -antichymotrypsin and  $\alpha_1$ -proteinase inhibitors protect the lung tissue from non-specific attack by the proteinases cathepsin G and elastase from polymorphonuclear lymphocytes. When the balance between proteases and their specific inhibitors is disturbed, pathological effects may arise. For example, an excess ratio of elastase to  $\alpha_1$ -proteinase inhibitor increases the risk of formation of a lung emphysema by a factor of about 20 to 30 in patients with a genetically caused deficiency in this factor as compared to the normal population (Carrel and Owen, 1980). With smokers, the formation of an emphysema is promoted by oxidation of the amino acid methionine which is present in the reactive site of the  $\alpha_1$ -proteinase inhibitor by oxidants contained in cigarette smoke (Miller and Kuschner, 1969; Ohlsson et al., 1980). Also in the case of infection with Gram-negative bacteria, their endotoxins can cause disintegration of phagocytes and thus the secretion of lysosomal proteases, which may cause an uncontrolled damage to tissues and inflammations due to the increased consumption of protease inhibitors. For this reason, certain protease inhibitors have a high therapeutic potential (see, e.g., Fritz, 1980).

International Application PCT/EP 98/08424 relates to serine protease inhibitors, wherein said serine protease inhibitors have a domain with four cysteines, and a sequence of from 0 to 20 amino acids is present between the first and second cysteines, or said serine protease inhibitors have a domain of six cysteines, and a sequence of from 7 to 20 amino acids is present between the first and second cysteines.

It has been the object of the present invention to provide further serine protease inhibitors.

This object is achieved by a serine protease inhibitor having the amino acid sequence according to SEQ ID NO: 1.

The present invention also relates to fragments of the serine protease inhibitor according to the invention having the amino acid sequence  $R_1$ -X- $R_2$ , wherein  $R_1$  is  $NH_2$ , an amino acid or a peptide with up to 100 amino acids, and  $R_2$  is  $COOH$ ,  $CONH_2$ , an amino acid or a peptide with up to 100 amino acids, and X is selected from SEQ ID NOS: 2 to 6.

It is preferred that the serine protease inhibitor contains one or more disulfide bridges. It is particularly preferred for it to contain a disulfide bridge between the first and fourth cysteines and/or between the second and third cysteines, or to contain a disulfide bridge between the first and fifth cysteines and/or between the second and fourth cysteines and/or between the third and sixth cysteines.

In addition to the amino acid sequence of the preferred compounds according to the invention, further information about the cDNA coding for the compounds according to the invention can also be seen from Figure 1. In particular, the corresponding motifs and primer-hybridizing sites are indicated.

According to the invention, nucleic acids coding for the compounds according to the invention, especially a DNA having the nucleic acid sequence according to SEQ ID NOS: 7 to 12, are also claimed.

The compounds according to the invention are useful as medicaments. In this case, they are administered together with pharmaceutically acceptable vehicles.

The medicaments according to the invention containing the protease inhibitors according to the invention are preferably administered in amounts of from 1 to 100 mg/kg of the patient's body weight. As the dosage form, all galenic formulations for peptide active substances may be used. The medicaments containing nucleic acids according to the invention are preferably administered in amounts of from 0.1 to 100 mg/kg of body weight of a corresponding patient. In this case, the galenic dosage forms which may be used are those which are suitable for the administration of nucleic acids without rendering the nucleic

acids ineffective by metabolic influences before they have reached their site of action. For example, liposomes in which the nucleic acids are contained can be employed as a galenic dosage form.

The compounds according to the invention can be used, in particular, for the treatment of acute or chronic cervix inflammations, inflammations of Bartholin's gland or other vaginal regions, tonsillitis, pharyngitis and laryngitis, acute or chronic inflammatory processes accompanied by excessive formation of mucus and the resulting acute emergency situations, postoperative bleedings due to hyperfibrinolysis, and for the prophylaxis of lung emphysema formation in deficiencies of  $\alpha_1$ -proteinase inhibitor.

Further, they may be employed for the therapy of asthma, AIDS, tumor diseases and leukemia.

The compounds according to the invention can be administered in deficiencies of serine protease inhibitors to correct endogenous defects. The nucleic acids may also be used in gene therapy, either directly or coupled to suitable vehicles. Suitable vectors include, in particular, attenuated adenoviruses into which the corresponding genes have been incorporated.

The polypeptides according to the invention can serve for the preparation of antibodies or antibody fragments. These are simply prepared by the immunization of appropriate mammals. By per se known operations, the antibodies may also be humanized so that such antibodies can also be employed for therapeutic use. Antibodies or antibody fragments can then be employed for the regulation of diseases in which the protease inhibitors are expressed in a pathological way. Also, antisense nucleic acids complementary to the nucleic acids according to the invention may be employed in therapeutical use in overexpressions of the protease inhibitor genes.

The compounds according to the invention can be easily prepared by per se known methods of peptide or nucleotide synthesis. Preparation of the compounds by genetic engineering is also possible.

Those skilled in the art will recognize that fragments of the polypeptides according to the invention may also be used provided that they retain the inhibitory properties of the serine protease inhibitors. Those skilled in the art know how to find such fragments. Thus, this may be accomplished, for example, by a selected enzymatic cleavage of the compounds according to the invention. Side-chain modified amino acids may also be employed. N- or C-terminally modified polypeptides may also be used. In particular, phosphorylated, glycosylated, methylated, acetylated or similarly modified polypeptides can be employed provided that they do not substantially affect the activity of the serine protease inhibitors.

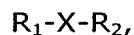
Derivatives of the nucleic acids according to the invention which have modified triplet structures in accordance with codon usage may also be used. In addition, nucleic acids according to the invention also include those which are more stable towards degradation by nucleases as compared with the native compounds, for example, the corresponding SODN derivatives usually employed in antisense technology to give the antisense structures a more stable design towards enzymatic attack.

Structures homologous to the polypeptides may also be used. In particular, these include polypeptide structures in which amino acids have been exchanged. Thus, for example, conservative amino acid substitutions in highly conserved regions can be considered as follows: any isoleucine, valine and leucine amino acid can be exchanged for any other of these amino acids, aspartate can be exchanged for glutamate and vice versa, glutamine for asparagine and vice versa, serine for threonine and vice versa. Conservative amino acid substitutions in less highly conserved regions can be as follows: Any of the amino acids isoleucine, valine and leucine for any other of these amino acids, aspartate for



CLAIMS:

1. A serine protease inhibitor having the amino acid sequence according to SEQ ID NO: 1.
2. A fragments of the serine protease inhibitor having the amino acid sequence



wherein  $R_1$  is  $NH_2$ , an amino acid or a peptide with up to 100 amino acids, and  $R_2$  is  $COOH$ ,  $CONH_2$ , an amino acid or a peptide with up to 100 amino acids, and X is selected from SEQ ID NOS: 2 to 6.

3. A nucleic acid coding for a serine protease inhibitor according to either of claims 1 or 2, especially SEQ ID NOS: 7 to 12.
4. A medicament containing at least one serine protease inhibitor according to claim 1 or 2 and/or a nucleic acid according to claim 3, optionally together with pharmaceutical vehicles.
5. The medicament according to claim 4, containing from 0.01 to 1000 mg per kg of body weight of the serine protease inhibitor according to claim 1 or 2 and/or of the nucleic acid according to claim 3.
6. Use of the medicament according to claim 1 or 2 for preparing a medicament for the treatment of acute or chronic cervix inflammations, inflammations of Bartholin's glands and other vaginal regions, tonsillitis, pharyngitis and laryngitis, acute or chronic inflammatory processes accompanied by excessive formation of mucus and the resulting acute emergency situations, postoperative bleedings due to hyperfibrinolysis,

and for the prophylaxis of lung emphysema formation in deficiencies of  $\alpha_1$ -proteinase inhibitor.

7. Use of the medicament according to claim 4 for the therapy of asthma, AIDS, pneumonia, tumor diseases and leukemia.
8. Use of the nucleic acids according to claim 3 for preparing a medicament for use in gene therapy for the curing and prophylaxis of diseases as mentioned in claim 6.
9. Antibodies or antibody fragments against epitopes of the compounds according to either of claims 1 or 2.
10. Poly- or oligonucleotides which will hybridize to regions of the cDNA or corresponding RNA under stringent conditions and optionally prevent the expression of coding regions of the genes coding for the compounds according to claims 1 or 2 (antisense compounds).
11. A diagnostic agent containing at least one of the compounds according to claim 9 or 10.
12. A medicament containing at least one of the compounds mentioned in claims 9 and/or 10 in therapeutically effective amounts.
13. Use of the compounds according to claims 9 and/or 10 for preparing a medicament for the treatment of diseases involving too high an expression of the compounds according to claim 1 or 2, or too high an activity of the regions coding for the compounds according to claim 1 or 2.
14. DNA, coding for the compounds mentioned in claim 1 or 2, and/or RNA involved in the transcription or translation of the compounds mentioned in claim 1 or 2.

The invention relates to serine protease inhibitors having the amino acid sequence in accordance with Seq. ID No. 1.



1/4

Figure 1

Frame 2

|                        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| ATG                    | CAT | GGA | GTG | GAC | CTG | TAG | GCG | ACT | TGC | ATC | GTC | TTC | AAC | ATG | K   | I   | A   |
|                        |     | 10  |     |     | 19  |     |     | 28  |     |     | 37  |     |     | 46  |     |     | 55  |
| T                      | V   | S   | V   | L   | L   | P   | L   | A   | L   | C   | L   | I   | Q   | D   | A   | A   | S   |
| ACA                    | GTG | TCA | GTG | CTT | CTG | CCC | TTG | GCT | CTT | TGC | CTC | ATA | CAA | GAT | GCT | GCC | AGT |
|                        |     | 64  |     |     | 73  |     |     | 82  |     |     | 91  |     |     | 100 |     |     | 109 |
| HF 6479                |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| K N                    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| AAG AAT                |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Repeat 1               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| E                      | D   | Q   | E   | M   | C   | H   | E   | F   | Q   | A   | F   | M   | K   | N   | G   | K   | L   |
| GAA                    | GAT | CAG | GAA | ATG | TGC | CAT | GAA | TTT | CAG | GCA | TTT | ATG | AAA | AAT | GGA | AAA | CTG |
|                        |     | 124 |     |     | 133 |     |     | 142 |     |     | 151 |     |     | 160 |     |     | 169 |
| P                      | Q   | D   | K   | K   | F   | F   | Q   | S   | L   | D   | G   | I   | M   | F   | I   | N   | K   |
| CCC                    | CAG | GAT | AAG | AAA | TTT | TTT | CAA | AGT | CTT | GAT | GGA | ATA | ATG | TTC | ATC | AAT | AAA |
|                        |     | 184 |     |     | 193 |     |     | 202 |     |     | 211 |     |     | 220 |     |     | 229 |
| HF 6479                |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| K S Q K R A R H L A    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| T                      | C   | K   | M   | I   | L   | E   | K   | E   | A   | K   | S   | Q   | K   | R   | A   | R   | H   |
| ACG                    | TGC | AAA | ATG | ATA | CTG | GAA | AAA | GAA | GCA | AAA | TCA | CAG | AAG | AGG | GCC | AGG | CAT |
|                        |     | 244 |     |     | 253 |     |     | 262 |     |     | 271 |     |     | 280 |     |     | 289 |
| typical Kazal domain 1 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| R                      | A   | P   | K   | A   | T   | A   | P   | T   | E   | L   | N   | C   | D   | D   | F   | K   | K   |
| AGA                    | GCT | CCC | AAG | GCT | ACT | GCC | CCA | ACA | GAG | CTG | AAT | TGT | GAT | GAT | TTT | AAA | AAA |
|                        |     | 304 |     |     | 313 |     |     | 322 |     |     | 331 |     |     | 340 |     |     | 349 |
| R                      | D   | G   | D   | F   | I   | C   | P   | D   | Y   | Y   | E   | A   | V   | C   | G   | T   | D   |
| AGA                    | GAT | GGG | GAT | TTT | ATC | TGT | CCT | GAT | TAT | TAT | GAA | GCT | GTT | TGT | GGC | ACA | GAT |
|                        |     | 364 |     |     | 373 |     |     | 382 |     |     | 391 |     |     | 400 |     |     | 409 |
| T                      | Y   | D   | N   | R   | C   | A   | L   | C   | A   | E   | N   | A   | K   | T   | G   | S   | Q   |
| ACA                    | TAT | GAC | AAC | AGA | TGT | GCA | CTG | TGT | GCT | GAG | AAT | GCG | AAA | ACC | GGG | TCC | CAA |
|                        |     | 424 |     |     | 433 |     |     | 442 |     |     | 451 |     |     | 460 |     |     | 469 |
| Repeat 2               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| V                      | K   | S   | E   | G   | E   | C   | K   | S   | S   | N   | P   | E   | Q   | D   | V   | C   | S   |
| GTA                    | AAA | AGT | GAA | GGG | GAA | TGT | AAG | AGC | AGT | AAT | CCA | GAG | CAG | GAT | GTA | TGC | AGT |
|                        |     | 484 |     |     | 493 |     |     | 502 |     |     | 511 |     |     | 520 |     |     | 529 |
| R                      | P   | F   | V   | R   | D   | G   | R   | L   | G   | C   | T   | R   | E   | N   | D   | P   | V   |
| CGG                    | CCC | TTT | GTT | AGA | GAT | GGA | AGA | CTT | GGA | TGC | ACA | AGG | GAA | AAT | GAT | CCT | GTT |
|                        |     | 544 |     |     | 553 |     |     | 562 |     |     | 571 |     |     | 580 |     |     | 589 |
| P                      | D   | G   | K   | T   | H   | G   | N   | K   | A   | M   | C   | A   | E   | L   | F   | L   | K   |
| CCT                    | GAT | GGG | AAG | ACG | CAT | GGC | AAT | AAG | TGT | GCA | ATG | TGT | GCT | GAG | CTG | TTT | TTA |
|                        |     | 604 |     |     | 613 |     |     | 622 |     |     | 631 |     |     | 640 |     |     | 649 |
| A                      | E   | N   | A   | K   | R   | E   | G   | E   | T   | R   | I   | R   | R   | N   | A   | E   | K   |
| GCT                    | GAA | AAT | GCC | AAG | CGA | GAG | GGT | GAA | ACT | AGA | ATT | CGA | CGA | AAT | GCT | GAA | AAG |
|                        |     | 664 |     |     | 673 |     |     | 682 |     |     | 691 |     |     | 700 |     |     | 709 |
| Repeat 3               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                      | K   | E   | Y   | E   | K   | Q   | V   | R   | N   | G   | R   | L   | F   | C   | T   | R   | E   |
| TGC                    | AAG | GAA | TAT | GAA | AAA | CAA | GTG | AGA | AAT | GGA | AGG | CTT | TTT | TGT | ACA | CGG | GAG |
|                        |     | 724 |     |     | 733 |     |     | 742 |     |     | 751 |     |     | 760 |     |     | 769 |
| P                      | V   | R   | G   | P   | D   | G   | R   | M   | H   | G   | N   | K   | C   | A   | L   | C   | A   |
| CCA                    | GTC | CGT | GGC | CCT | GAC | GGC | AGG | ATG | CAT | GGC | AAC | AAA | TGT | GCC | CTG | TGT | GCT |
|                        |     | 784 |     |     | 793 |     |     | 802 |     |     | 811 |     |     | 820 |     |     | 829 |
| F                      | K   | R   | R   | F   | S   | E   | E   | N   | S   | K   | T   | D   | Q   | N   | L   | G   | K   |
| TTC                    | AAG | CGG | CGT | TTT | TCA | EAG | GAA | AAC | AGT | AAA | ACA | GAT | CAA | AAT | TTG | GGA | AAA |
|                        |     | 844 |     |     | 853 |     |     | 862 |     |     | 871 |     |     | 880 |     |     | 889 |
| Repeat 4               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| E                      | K   | T   | K   | V   | K   | R   | E   | I   | V   | K   | L   | C   | S   | Q   | Y   | Q   | N   |
| GAA                    | AAA | ACT | AAA | GTT | AAA | AGA | GAA | ATT | GTG | AAA | CTC | TGC | AGT | CAA | TAT | CAA | AAT |
|                        |     | 904 |     |     | 913 |     |     | 922 |     |     | 931 |     |     | 940 |     |     | 949 |

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|     |     |     |     |     |     |   |     |     |     |     |     |     |     |     |      |     |     |      |     |     |
|-----|-----|-----|-----|-----|-----|---|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|------|-----|-----|
| K   | N   | G   | I   | L   | F   | # | C   | T   | R   | E   | N   | D   | P   | I   | R    | G   | P   | D    | G   | K   |
| AAG | AAT | GGA | ATA | CTT | TTC |   | TGT | ACC | AGA | GAA | AAT | GAC | CCT | ATT | CGT  | GGT | CCA | GAT  | GGG | AAA |
|     |     | 964 |     |     | 973 |   |     |     | 982 |     |     | 991 |     |     | 1000 |     |     | 1009 |     |     |

|     |     |      |     |     |      |   |     |     |      |     |     |      |     |     |      |     |     |      |     |     |
|-----|-----|------|-----|-----|------|---|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|
| M   | H   | G    | N   | L   | C    | # | S   | M   | C    | Q   | V   | Y    | F   | Q   | A    | E   | N   | E    | E   | K   |
| ATG | CAT | GGC  | AAC | TTG | TGT  |   | TCC | ATG | TGT  | CAA | GTC | TAC  | TTC | CAA | GCA  | GAA | AAT | GAA  | GAA | AAG |
|     |     | 1024 |     |     | 1033 |   |     |     | 1042 |     |     | 1051 |     |     | 1060 |     |     | 1069 |     |     |

|     |     |      |     |     |      |     |     |      |     |     |         |   |      |   |   |      |   |   |      |  |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|---------|---|------|---|---|------|---|---|------|--|
| K   | K   | A    | E   | A   | R    | A   | R   | N    | K   | R   | HF 7665 |   |      |   |   |      |   |   |      |  |
| AAA | AAG | GCT  | GAA | GCA | CGA  | GCT | AGA | AAC  | AAA | AGA | E       | S | G    | K | A | T    | S | Y | A    |  |
|     |     | 1084 |     |     | 1093 |     |     | 1102 |     |     |         |   | 1111 |   |   | 1120 |   |   | 1129 |  |

Repeat 5

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |   |     |      |     |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|---|-----|------|-----|-----|
| E   | L   | C    | N   | E   | Y    | R   | K   | L    | V   | R   | N    | G   | K   | L    | A   | # | C   | T    | R   | E   |
| GAG | CTT | TGC  | AAT | GAA | TAT  | CGA | AAG | CTT  | GTG | AGG | AAC  | GGA | AAA | CTT  | GCT |   | TGC | ACC  | AGA | GAG |
|     |     | 1144 |     |     | 1153 |     |     | 1162 |     |     | 1171 |     |     | 1180 |     |   |     | 1189 |     |     |

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |   |     |      |     |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|---|-----|------|-----|-----|
| N   | D   | P    | I   | Q   | G    | P   | D   | G    | K   | V   | H    | G   | N   | T    | C   | # | S   | M    | C   | E   |
| AAC | GAT | CCT  | ATC | CAG | GGC  | CCA | GAT | GGG  | AAA | GTG | CAC  | GGC | AAC | ACC  | TGC |   | TCC | ATG  | TGT | GAG |
|     |     | 1204 |     |     | 1213 |     |     | 1222 |     |     | 1231 |     |     | 1240 |     |   |     | 1249 |     |     |

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |     |     |      |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|
| V   | F   | F    | Q   | A   | E    | E   | E   | E    | K   | K   | K    | K   | E   | G    | E   | S   | R   | N    | K   |
| GTC | TTC | TTC  | CAA | GCA | GAA  | GAA | GAA | AAG  | AAA | AAG | AAG  | AAG | GAA | GGC  | GAA | TCA | AGA | AAC  | AAA |
|     |     | 1264 |     |     | 1273 |     |     | 1282 |     |     | 1291 |     |     | 1300 |     |     |     | 1309 |     |

Repeat 6

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |     |     |      |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|
| R   | Q   | S    | K   | S   | T    | A   | S   | F    | E   | E   | L    | C   | S   | E    | Y   | R   | K   | S    | R   |
| AGA | CAA | TCT  | AAG | AGT | ACA  | GCT | TCC | TTT  | GAG | GAG | TTG  | TGT | AGT | GAA  | TAC | CGC | AAA | TCC  | AGG |
|     |     | 1324 |     |     | 1333 |     |     | 1342 |     |     | 1351 |     |     | 1360 |     |     |     | 1369 |     |

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |     |     |      |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|
| K   | N   | G    | R   | L   | F    | C   | T   | R    | E   | N   | D    | P   | I   | Q    | G   | P   | D   | G    | K   |
| AAA | AAC | GGA  | CGG | CTT | TTT  | TGC | ACC | AGA  | GAG | AAT | GAC  | CCC | ATC | CAG  | GGC | CCA | GAT | GGG  | AAA |
|     |     | 1384 |     |     | 1393 |     |     | 1402 |     |     | 1411 |     |     | 1420 |     |     |     | 1429 |     |

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |     |     |      |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|
| M   | H   | G    | N   | T   | C    | S   | M   | C    | E   | A   | F    | F   | Q   | Q    | E   | E   | R   | A    | R   |
| ATG | CAT | GGC  | AAC | ACC | TGC  | TCC | ATG | TGT  | GAG | GCC | TTC  | TTT | CAA | CAA  | GAA | GAA | AGA | GCA  | AGA |
|     |     | 1444 |     |     | 1453 |     |     | 1462 |     |     | 1471 |     |     | 1480 |     |     |     | 1489 |     |

Repeat 7

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |     |     |      |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|
| A   | K   | A    | K   | R   | E    | A   | A   | K    | E   | I   | C    | S   | E   | F    | R   | D   | Q   | V    | R   |
| GCA | AAG | GCT  | AAA | AGA | GAA  | GCT | GCA | AAG  | GAA | ATC | TGC  | AGT | GAA | TTT  | CGG | GAC | CAA | GTG  | AGG |
|     |     | 1504 |     |     | 1513 |     |     | 1522 |     |     | 1531 |     |     | 1540 |     |     |     | 1549 |     |

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |     |     |      |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|
| N   | G   | T    | L   | I   | C    | T   | R   | E    | H   | N   | P    | V   | R   | G    | P   | D   | G   | K    | M   |
| AAT | GGA | ACA  | CTT | ATA | TGC  | ACC | AGG | GAG  | CAT | AAT | CCT  | GTC | CGT | GGA  | CCA | GAT | GGC | AAA  | ATG |
|     |     | 1564 |     |     | 1573 |     |     | 1582 |     |     | 1591 |     |     | 1600 |     |     |     | 1609 |     |

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |     |     |      |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|
| H   | G   | N    | K   | C   | A    | M   | C   | A    | S   | V   | F    | K   | L   | E    | E   | E   | E   | K    | K   |
| CAT | GGA | AAC  | AAG | TGT | GCC  | ATG | TGT | GCC  | AGT | GTG | TTC  | AAA | CTT | GAA  | GAA | GAA | GAG | AAG  | AAA |
|     |     | 1624 |     |     | 1633 |     |     | 1642 |     |     | 1651 |     |     | 1660 |     |     |     | 1669 |     |

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |     |     |      |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|
| N   | D   | K    | E   | E   | K    | G   | K   | V    | E   | A   | E    | K   | V   | K    | R   | E   | A   | V    | Q   |
| AAT | GAT | AAA  | GAA | GAA | AAA  | GGG | AAA | GTT  | GAG | GCT | GAA  | AAA | GTT | AAG  | AGA | GAA | GCA | GTT  | CAG |
|     |     | 1684 |     |     | 1693 |     |     | 1702 |     |     | 1711 |     |     | 1720 |     |     |     | 1729 |     |

Repeat 8

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |   |     |      |     |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|---|-----|------|-----|-----|
| E   | L   | C    | S   | E   | Y    | R   | H   | Y    | V   | R   | N    | G   | R   | L    | P   | # | C   | T    | R   | E   |
| GAG | CTG | TGC  | AGT | GAA | TAT  | CGT | CAT | TAT  | GTG | AGG | AAT  | GGA | CGA | CTC  | CCC |   | TGT | ACC  | AGA | GAG |
|     |     | 1744 |     |     | 1753 |     |     | 1762 |     |     | 1771 |     |     | 1780 |     |   |     | 1789 |     |     |

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |   |     |      |     |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|---|-----|------|-----|-----|
| N   | D   | P    | I   | E   | G    | L   | D   | G    | K   | I   | H    | G   | N   | T    | C   | # | S   | M    | C   | E   |
| AAT | GAT | CCT  | ATT | GAG | GGT  | CTA | GAT | GGG  | AAA | ATC | CAC  | GGC | AAC | ACC  | TGC |   | TCC | ATG  | TGT | GAA |
|     |     | 1804 |     |     | 1813 |     |     | 1822 |     |     | 1831 |     |     | 1840 |     |   |     | 1849 |     |     |

|     |     |      |     |     |      |     |     |      |     |     |      |     |     |      |     |     |     |      |     |
|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|
| A   | F   | F    | Q   | Q   | E    | A   | K   | E    | K   | E   | R    | A   | E   | P    | R   | A   | K   | V    | K   |
| GCC | TTC | TTC  | CAG | CAA | GAA  | GCA | AAA | GAA  | AAA | GAA | AGA  | GCT | GAA | CCC  | AGA | GCA | AAA | GTC  | AAA |
|     |     | 1864 |     |     | 1873 |     |     | 1882 |     |     | 1891 |     |     | 1900 |     |     |     | 1909 |     |

Repeat 9

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R | E | A | E | K | E | T | C | D | E | F | R | R | L | L | Q | N | G | K | L |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

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AGA GAA GCT GAA AAG GAG ACA TGC GAT GAA TTT CGG AGA CTT TTG CAA AAT GGA AAA CTT  
 1924 1933 1942 1951 1960 1969

#  
 F C T R E N D P V R G P D G K T H G N K  
 TTC TGC ACA AGA GAA AAT GAT CCT GTG CGT GGC CCA GAT GGC AAG ACC CAT GGC AAC AAG  
 1984 1993 2002 2011 2020 2029

#  
 C A M C K A V F Q K E N E E R K R K E E  
 TGT GCC ATG TGT AAG GCA GTC TTC CAG AAA GAA AAT GAG GAA AGA AAG AGG AAA GAA GAG  
 2044 2053 2062 2071 2080 2089

E D Q R N A A G H G S S G G G G N T Q  
 GAA GAT CAG AGA AAT GCT GCA GGA CAT GGT TCC AGT GGT GGT GGA GGA GGA AAC ACT CAG  
 2104 2113 2122 2131 2140 2149

Repeat 10  
 \*  
 D E C A E Y Q E Q M K N G R L S C T R E  
 GAC GAA TGT GCT GAG TAT CAG GAA CAA ATG AAA AAT GGA AGA CTC AGC TGT ACT CGG GAG  
 2164 2173 2182 2191 2200 2209

#  
 S D P V R D A D G K S Y N N Q C T M C K  
 AGT GAT CCT GTA CGT GAT GCT GAT GGC AAA TCG TAC AAC AAT CAG TGT ACC ATG TGT AAA  
 2224 2233 2242 2251 2260 2269

A K L E R E A E R K N E Y S R S R S N G  
 GCA AAA TTG GAA AGA GAA GCA GAG AGA AAA AAT GAG TAT TCT CGC TCC AGA TCA AAT GGG  
 2284 2293 2302 2311 2320 2329

Repeat 11  
 \*  
 T G S E S G K D T C D E F R S Q M K N G  
 ACT GGA TCA GAA TCA GGG AAG GAT ACA TGT GAT GAG TTT AGA AGC CAA ATG AAA AAT GGA  
 2344 2353 2362 2371 2380 2389

#  
 K L I C T R E S D P V R G P D G K T H G  
 AAA CTT ATC TGC ACT CGA GAA AGT GAC CCT GTC CGG GGT CCA GAT GGC AAG ACA CAT GGT  
 2404 2413 2422 2431 2440 2449

#  
 N K C T M C K E K L E R E A A E K K K K  
 AAT AAG TGT ACT ATG TGT AAG GAA AAA CTG GAA AGG GAA GCA GCT GAA AAA AAA AAG AAA  
 2464 2473 2482 2491 2500 2509

E D E D R S N T G E R S N T G E R S N D  
 GAG GAT GAA GAC AGG AGC AAT ACA GGA GAA AGG AGC AAT ACA GGA GAA AGG AGC AAT GAC  
 2524 2533 2542 2551 2560 2569

Repeat 12  
 \*  
 K E D L C R E F R S M Q R N G K L I C T  
 AAA GAG GAT CTG TGT CGT GAA TTT CGA AGC ATG CAG AGA AAT GGA AAG CTT ATC TGC ACC  
 2584 2593 2602 2611 2620 2629

#  
 R E N N P V R G P Y G K M H I N K C A M  
 AGA GAA AAT AAC CCT GTT CGA GGC CCA TAT GGC AAG ATG CAC ATC AAT AAA TGT GCT ATG  
 2644 2653 2662 2671 2680 2689

#  
 C Q S I F D R E A N E R K K K D E E K S  
 TGT CAG AGC ATC TTT GAT CGA GAA GCT AAT GAA AGA AAA AAG AAA GAT GAA GAG AAA TCA  
 2704 2713 2722 2731 2740 2749

Repeat 13  
 \*  
 S S K P S N N A K D E C S E F R N Y I R  
 AGT AGC AAG CCC TCA AAT AAT GCA AAG GAT GAG TGC AGT GAA TTT CGA AAC TAT ATA AGG  
 2764 2773 2782 2791 2800 2809

#  
 N N E L I C P R E N D P V H G A D G K F  
 AAC AAT GAA CTC ATC TGC CCT AGA GAG AAT GAC CCA GTG CAC GGT GCT GAT GGA AAG TTC  
 2824 2833 2842 2851 2860 2869

#  
 Y T N K C Y M C R A V F L T E A L E R A  
 TAT ACA AAC AAG TGC TAC ATG TGC AGA GCT GTC TTT CTA ACA GAA GCT TTG GAA AGG GCA  
 2884 2893 2902 2911 2920 2929

K L Q E K P S H V R A S Q E E D S P D S  
 AAG CTT CAA GAA AAG CCA TCC CAT GTT AGA GCT TCT CAA GAG GAA GAC AGC CCA GAC TCT  
 2944 2953 2962 2971 2980 2989

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      *
F   S   S   L   D   S   E   M   C   K   D   Y   R   V   L   P   R   I   G   Y
TTC AGT TCT CTG GAT TCT GAG ATG TGC AAA GAC TAC CGA GTA TTG CCC AGG ATA GGC TAT
      3004      3013      3022      3031      3040      3049
#
L   C   P   K   D   L   K   P   V   C   G   D   D   G   Q   T   Y   N   N   P
CTT TGT CCA AAG GAT TTA AAG CCT GTC TGT GGT GAC GAT GGC CAA ACC TAC AAC AAT CCT
      3064      3073      3082      3091      3100      3109
#
C   M   L   C   H   E   N   L   I   R   Q   T   N   T   H   I   R   S   T   G
TGC ATG CTC TGT CAT GAA AAC CTG ATA CGC CAA ACA AAT ACA CAC ATC CGC AGT ACA GGG
      3124      3133      3142      3151      3160      3169
+
K   C   E   E   S   S   T   P   G   T   T   A   A   S   M   P   P   S   D   E
AAG TGT GAG GAG AGC AGC ACC CCA GGA ACC ACC GCA GCC AGC ATG CCC CCG TCT GAC GAA
      3184      3193      3202      3211      3220      3229

TGA CAG GAA GAT TGT TGA AAG CCA TGA GGG AAA AAA TAA ACC CCA GTT CTG AAT CAC CTA
      3244      3253      3262      3271      3280      3289

CCT TCA CCA TCT GTA TAT ACA AAG AAT TCT TCG GAG CTT GTC TTA TTT GCT ATA GAA AAC
      3304      3313      3322      3331      3340      3349

AAT ACA GAG CTT TTG GGA ATG GAA TCA CTG ATT TTC AGT CTT TTC CAT TTC TTT CCT CCT
      3364      3373      3382      3391      3400      3409

AGA ATC TGT GAT CTG AGG GTA TAA AGA CAT TTC CAC CAA GTT TGA GCC CTC AAA ATG TCC
      3424      3433      3442      3451      3460      3469

TGA TTA CAA TGC TGT CTG TCC AAC TGC CTG TTC AAT AAA AGT AAA CTC AGC AGA AAA....
      3484      3493      3502      3511      3520      3529
polyadenylation signal

```

.....poly(A) tail

The following sequence corrections have been performed:

An additional A in position 2510 results in a frame shift which produces three additional inhibitor domains.

Base were exchanged in ten different positions:

```

Position 551:  G for A
Position 1207: C for T
Position 1258: C for T
Position 1261: C for T
Position 2175: A for G
Position 2950: G for A
Position 3228: C for T
Position 3284: C for T
Position 3324: C for T
Position 3337: C for T

```

SEQUENZPROTOKOLL

&lt;110&gt; Forssmann Prof., Wolf-Georg

&lt;120&gt; Serin-Proteinase-Inhibitoren

&lt;130&gt; Forssmann

&lt;140&gt;

&lt;141&gt;

&lt;160&gt; 12

&lt;170&gt; PatentIn Ver. 2.1

&lt;210&gt; 1

DECLARATION  
AND POWER OF ATTORNEY  
U.S.A.

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ATTORNEYS' DOCKET NO.

ALL PATENTS, INCLUDING DESIGN  
FOR APPLICATION BASED ON PCT, PARIS CONVENTION,  
NON PRIORITY, OR PROVISIONAL APPLICATIONS

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or an original, first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

Serine Protease Inhibitors

which is described and claimed in: ☒ PCT International Application No. PCT/EP99/04331 filed June 22, 1999  
☐ the attached specification ☐ the specification in application Serial No. \_\_\_\_\_ filed \_\_\_\_\_  
(if applicable) and amended on \_\_\_\_\_

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Priority Claimed

| (Number) | (Country) | (Day/Month/Year Filed) | Yes                      | No                       |
|----------|-----------|------------------------|--------------------------|--------------------------|
| ____     | ____      | ____                   | <input type="checkbox"/> | <input type="checkbox"/> |
| ____     | ____      | ____                   | <input type="checkbox"/> | <input type="checkbox"/> |
| ____     | ____      | ____                   | <input type="checkbox"/> | <input type="checkbox"/> |

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application No. \_\_\_\_\_ Filing Date \_\_\_\_\_ Application No. \_\_\_\_\_ Filing Date \_\_\_\_\_

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)

(Filing Date)

(Status: patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No. ) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851), JOHN CLARKE HOLMAN (22,769), MARVIN R. STERN (20,640), ALLEN S. MELSER (27,215), MICHAEL R. SLOBASKY (28,421), JONATHAN L. SCHERER (29,851), IRWIN M. AISENBERG (19,007), WILLIAM E. PLAYER (31,409), YOON S. HAM (45,307) and NATHANIEL A. HUMPHRIES (22,772)

SEND CORRESPONDENCE TO CUSTOMER NO. 00136

or

JACOBSON HOLMAN  
PROFESSIONAL LIMITED LIABILITY COMPANY  
400 SEVENTH STREET, N.W.  
WASHINGTON, D.C. 20004

DIRECT TELEPHONE CALLS TO:

(please use Attorney's Docket No.) (202) 638-6666

JACOBSON HOLMAN  
PROFESSIONAL LIMITED LIABILITY COMPANY

\*Inventor(s) name must include at least one unabbreviated first or middle name.

|     | FULL NAME* OF INVENTOR  | FAMILY NAME         | GIVEN NAME               | MIDDLE NAME            |
|-----|-------------------------|---------------------|--------------------------|------------------------|
| 201 | RESIDENCE & CITIZENSHIP | CITY                | STATE OR FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP |
|     | POST OFFICE ADDRESS     | POST OFFICE ADDRESS | CITY                     | STATE OR COUNTRY       |
|     |                         |                     |                          | ZIP CODE               |
| 202 | RESIDENCE & CITIZENSHIP | CITY                | STATE OR FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP |
|     | POST OFFICE ADDRESS     | POST OFFICE ADDRESS | CITY                     | STATE OR COUNTRY       |
|     |                         |                     |                          | ZIP CODE               |
| 203 | RESIDENCE & CITIZENSHIP | CITY                | STATE OR FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP |
|     | POST OFFICE ADDRESS     | POST OFFICE ADDRESS | CITY                     | STATE OR COUNTRY       |
|     |                         |                     |                          | ZIP CODE               |

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

| SIGNATURE OF INVENTOR 201* | SIGNATURE OF INVENTOR 202* | SIGNATURE OF INVENTOR 203* |
|----------------------------|----------------------------|----------------------------|
| DATE 12/13/2001            | DATE 13.12.2001            | DATE 13.12.2001            |

☐ Additional inventors are named on separately numbered sheets attached hereto.

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DECLARATION  
AND POWER OF ATTORNEY  
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ATTORNEYS' DOCKET NO.

- ALL PATENTS, INCLUDING DESIGN  
FOR APPLICATION BASED ON PCT; PARIS CONVENTION;  
NON PRIORITY; OR PROVISIONAL APPLICATIONS

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or an original, first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

Serine Protease Inhibitors

which is described and claimed in: ☒ PCT International Application No. PCT/EP99/04331 filed June 22, 1999  
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Prior Foreign Application(s)

(Number) \_\_\_\_\_ (Country) \_\_\_\_\_ (Day/Month/Year Filed) \_\_\_\_\_

Priority Claimed

☐ Yes ☐ No

(Number) \_\_\_\_\_ (Country) \_\_\_\_\_ (Day/Month/Year Filed) \_\_\_\_\_

☐ Yes ☐ No

(Number) \_\_\_\_\_ (Country) \_\_\_\_\_ (Day/Month/Year Filed) \_\_\_\_\_

☐ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application No. \_\_\_\_\_ Filing Date \_\_\_\_\_ Application No. \_\_\_\_\_ Filing Date \_\_\_\_\_

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(Filing Date)

(Status: patented, pending, abandoned)

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(please use Attorney's Docket No.) (202) 638-6666

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\*Inventor(s) name must include at least one unabbreviated first or middle name.

|     | FULL NAME *<br>OF INVENTOR | FAMILY NAME | GIVEN NAME               | MIDDLE NAME            |
|-----|----------------------------|-------------|--------------------------|------------------------|
| 201 | RESIDENCE & CITIZENSHIP    | CITY        | STATE OR FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP |
|     | POST OFFICE ADDRESS        | CITY        | STATE OR COUNTRY         | ZIP CODE               |
| 202 | FULL NAME *<br>OF INVENTOR | FAMILY NAME | GIVEN NAME               | MIDDLE NAME            |
|     | RESIDENCE & CITIZENSHIP    | CITY        | STATE OR FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP |
|     | POST OFFICE ADDRESS        | CITY        | STATE OR COUNTRY         | ZIP CODE               |
| 203 | FULL NAME *<br>OF INVENTOR | FAMILY NAME | GIVEN NAME               | MIDDLE NAME            |
|     | RESIDENCE & CITIZENSHIP    | CITY        | STATE OR FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP |
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| SIGNATURE OF INVENTOR 201* | SIGNATURE OF INVENTOR 202* | SIGNATURE OF INVENTOR 203* |
|----------------------------|----------------------------|----------------------------|
| DATE                       | DATE                       | DATE                       |

☐ Additional inventors are named on separately numbered sheets attached hereto.

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## SEQUENCE LISTING

<110> FORSSMANN, WOLF-GEORG  
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STANDKER, LUDGER  
KREUTZMANN, PETER

<120> SERINE PROTEASE INHIBITORS

<130> 10496-P67431US0

<140> 09/926,820

<141> 2001-12-26

<150> PCT/EP99/04331

<151> 1999-06-22

<160> 12

<170> PatentIn Ver. 2.1

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Phe Gln Ala Phe Met Lys Asn Gly Lys Leu Phe Cys Pro Gln Asp Lys
      35              40              45

Lys Phe Phe Gln Ser Leu Asp Gly Ile Met Phe Ile Asn Lys Cys Ala
      50              55              60

Thr Cys Lys Met Ile Leu Glu Lys Glu Ala Lys Ser Gln Lys Arg Ala
      65              70              75              80

Arg His Leu Ala Arg Ala Pro Lys Ala Thr Ala Pro Thr Glu Leu Asn
      85              90              95

Cys Asp Asp Phe Lys Lys Gly Glu Arg Asp Gly Asp Phe Ile Cys Pro
      100              105              110

Asp Tyr Tyr Glu Ala Val Cys Gly Thr Asp Gly Lys Thr Tyr Asp Asn
      115              120              125

Arg Cys Ala Leu Cys Ala Glu Asn Ala Lys Thr Gly Ser Gln Ile Gly
      130              135              140

Val Lys Ser Glu Gly Glu Cys Lys Ser Ser Asn Pro Glu Gln Asp Val
      145              150              155              160
```

|            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
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| Arg        | Glu        | Asn        | Asp<br>180 | Pro        | Val        | Leu        | Gly        | Pro<br>185 | Asp        | Gly        | Lys        | Thr        | His        | Gly        | Asn        |
| Lys        | Cys        | Ala<br>195 | Met        | Cys        | Ala        | Glu        | Leu<br>200 | Phe        | Leu        | Lys        | Glu        | Ala<br>205 | Glu        | Asn        | Ala        |
| Lys        | Arg<br>210 | Glu        | Gly        | Glu        | Thr        | Arg<br>215 | Ile        | Arg        | Arg        | Asn        | Ala<br>220 | Glu        | Lys        | Asp        | Phe        |
| Cys<br>225 | Lys        | Glu        | Tyr        | Glu        | Lys<br>230 | Gln        | Val        | Arg        | Asn        | Gly<br>235 | Arg        | Leu        | Phe        | Cys        | Thr<br>240 |
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| Lys        | Cys        | Ala        | Leu<br>260 | Cys        | Ala        | Glu        | Ile        | Phe<br>265 | Lys        | Arg        | Arg        | Phe        | Ser<br>270 | Glu        | Glu        |
| Asn        | Ser        | Lys<br>275 | Thr        | Asp        | Gln        | Asn        | Leu<br>280 | Gly        | Lys        | Ala        | Glu        | Glu<br>285 | Lys        | Thr        | Lys        |
| Val        | Lys<br>290 | Arg        | Glu        | Ile        | Val        | Lys<br>295 | Leu        | Cys        | Ser        | Gln        | Tyr<br>300 | Gln        | Asn        | Gln        | Ala        |
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| Pro        | Asp        | Gly        | Lys        | Met<br>325 | His        | Gly        | Asn        | Leu        | Cys<br>330 | Ser        | Met        | Cys        | Gln        | Val<br>335 | Tyr        |
| Phe        | Gln        | Ala        | Glu<br>340 | Asn        | Glu        | Glu        | Lys        | Lys<br>345 | Lys        | Ala        | Glu        | Ala        | Arg<br>350 | Ala        | Arg        |
| Asn        | Lys        | Arg<br>355 | Glu        | Ser        | Gly        | Lys        | Ala<br>360 | Thr        | Ser        | Tyr        | Ala        | Glu<br>365 | Leu        | Cys        | Asn        |
| Glu        | Tyr<br>370 | Arg        | Lys        | Leu        | Val        | Arg<br>375 | Asn        | Gly        | Lys        | Leu        | Ala<br>380 | Cys        | Thr        | Arg        | Glu        |
| Asn<br>385 | Asp        | Pro        | Ile        | Gln        | Gly<br>390 | Pro        | Asp        | Gly        | Lys        | Val<br>395 | His        | Gly        | Asn        | Thr        | Cys<br>400 |
| Ser        | Met        | Cys        | Glu        | Val<br>405 | Phe        | Phe        | Gln        | Ala        | Glu<br>410 | Glu        | Glu        | Glu        | Lys        | Lys<br>415 | Lys        |
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| Phe        | Glu        | Glu<br>435 | Leu        | Cys        | Ser        | Glu        | Tyr<br>440 | Arg        | Lys        | Ser        | Arg        | Lys<br>445 | Asn        | Gly        | Arg        |
| Leu        | Phe<br>450 | Cys        | Thr        | Arg        | Glu        | Asn<br>455 | Asp        | Pro        | Ile        | Gln        | Gly<br>460 | Pro        | Asp        | Gly        | Lys        |



|            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
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| Glu        | His        | Asn<br>515 | Pro        | Val        | Arg        | Gly        | Pro<br>520 | Asp        | Gly        | Lys        | Met        | His<br>525 | Gly        | Asn        | Lys        |
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| Glu        | Ala        | Val        | Gln<br>565 | Glu        | Leu        | Cys        | Ser        | Glu        | Tyr<br>570 | Arg        | His        | Tyr        | Val        | Arg<br>575 | Asn        |
| Gly        | Arg        | Leu        | Pro<br>580 | Cys        | Thr        | Arg        | Glu        | Asn<br>585 | Asp        | Pro        | Ile        | Glu        | Gly<br>590 | Leu        | Asp        |
| Gly        | Lys        | Ile<br>595 | His        | Gly        | Asn        | Thr        | Cys<br>600 | Ser        | Met        | Cys        | Glu        | Ala<br>605 | Phe        | Phe        | Gln        |
| Gln<br>610 | Glu        | Ala        | Lys        | Glu        | Lys        | Glu<br>615 | Arg        | Ala        | Glu        | Pro        | Arg<br>620 | Ala        | Lys        | Val        | Lys        |
| Arg<br>625 | Glu        | Ala        | Glu        | Lys        | Glu<br>630 | Thr        | Cys        | Asp        | Glu        | Phe<br>635 | Arg        | Arg        | Leu        | Leu        | Gln<br>640 |
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| Gln        | Lys        | Glu<br>675 | Asn        | Glu        | Glu        | Arg        | Lys<br>680 | Arg        | Lys        | Glu        | Glu        | Glu<br>685 | Asp        | Gln        | Arg        |
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| Asp<br>705 | Glu        | Cys        | Ala        | Glu        | Tyr<br>710 | Gln        | Glu        | Gln        | Met        | Lys<br>715 | Asn        | Gly        | Arg        | Leu        | Ser<br>720 |
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| Asn        | Asn        | Gln<br>740 | Cys        | Thr        | Met        | Cys        | Lys        | Ala<br>745 | Lys        | Leu        | Glu        | Arg        | Glu<br>750 | Ala        | Glu        |
| Arg        | Lys<br>755 | Asn        | Glu        | Tyr        | Ser        | Arg        | Ser<br>760 | Arg        | Ser        | Asn        | Gly<br>765 | Thr        | Gly        | Ser        | Glu        |

Ser Gly Lys Asp Thr Cys Asp Glu Phe Arg Ser Gln Met Lys Asn Gly  
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 Lys Leu Ile Cys Thr Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly  
 785 790 795 800  
 Lys Thr His Gly Asn Lys Cys Thr Met Cys Lys Glu Lys Leu Glu Arg  
 805 810 815  
 Glu Ala Ala Glu Lys Lys Lys Lys Glu Asp Glu Asp Arg Ser Asn Thr  
 820 825 830  
 Gly Glu Arg Ser Asn Thr Gly Glu Arg Ser Asn Asp Lys Glu Asp Leu  
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 Cys Arg Glu Phe Arg Ser Met Gln Arg Asn Gly Lys Leu Ile Cys Thr  
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 980 985 990  
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      20              25              30

Cys Ala Met
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|---------|------|-----|-----|------|------|-----|-----|------|-----|-----|-------|-----|-----|-----|-----|-----|----|
| <400> 7 |      |     |     |      |      |     |     |      |     |     |       |     |     |     |     |     |    |
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|         |      |     |     |      |      |     |     |      |     |     |       |     | Met | Lys | Ile | Ala |    |
|         |      |     |     |      |      |     |     |      |     |     |       |     | 1   |     |     |     |    |
|         |      |     |     |      |      |     |     |      |     |     |       |     |     |     |     |     |    |
| aca     | gtg  | tca | gtg | ctt  | ctg  | ccc | ttg | gct  | ctt | tgc | ctc   | ata | caa | gat | gct | 103 |    |
| Thr     | Val  | Ser | Val | Leu  | Leu  | Pro | Leu | Ala  | Leu | Cys | Leu   | Ile | Gln | Asp | Ala |     |    |
| 5       |      |     |     |      | 10   |     |     |      |     | 15  |       |     |     |     | 20  |     |    |
|         |      |     |     |      |      |     |     |      |     |     |       |     |     |     |     |     |    |
| gcc     | agt  | aag | aat | gaa  | gat  | cag | gaa | atg  | tgc | cat | gaa   | ttt | cag | gca | ttt | 151 |    |
| Ala     | Ser  | Lys | Asn | Glu  | Asp  | Gln | Glu | Met  | Cys | His | Glu   | Phe | Gln | Ala | Phe |     |    |
|         |      |     |     | 25   |      |     |     |      | 30  |     |       |     |     | 35  |     |     |    |
|         |      |     |     |      |      |     |     |      |     |     |       |     |     |     |     |     |    |
| atg     | aaa  | aat | gga | aaa  | ctg  | ttc | tgt | ccc  | cag | gat | aag   | aaa | ttt | ttt | caa | 199 |    |
| Met     | Lys  | Asn | Gly | Lys  | Leu  | Phe | Cys | Pro  | Gln | Asp | Lys   | Lys | Phe | Phe | Gln |     |    |
|         |      |     | 40  |      |      |     |     | 45   |     |     |       |     | 50  |     |     |     |    |
|         |      |     |     |      |      |     |     |      |     |     |       |     |     |     |     |     |    |
| agt     | ctt  | gat | gga | ata  | atg  | ttc | atc | aat  | aaa | tgt | gcc   | acg | tgc | aaa | atg | 247 |    |
| Ser     | Leu  | Asp | Gly | Ile  | Met  | Phe | Ile | Asn  | Lys | Cys | Ala   | Thr | Cys | Lys | Met |     |    |
|         |      | 55  |     |      |      |     | 60  |      |     |     |       | 65  |     |     |     |     |    |

|   |     |
|---|-----|
| ata ctg gaa aaa gaa gca aaa tca cag aag agg gcc agg cat tta gca | 295 |
| Ile Leu Glu Lys Glu Ala Lys Ser Gln Lys Arg Ala Arg His Leu Ala |     |
| 70 75 80  |     |
| aga gct ccc aag gct act gcc cca aca gag ctg aat tgt gat gat ttt | 343 |
| Arg Ala Pro Lys Ala Thr Ala Pro Thr Glu Leu Asn Cys Asp Asp Phe |     |
| 85 90 95 100  |     |
| aaa aaa gga gaa aga gat ggg gat ttt atc tgt cct gat tat tat gaa | 391 |
| Lys Lys Gly Glu Arg Asp Gly Asp Phe Ile Cys Pro Asp Tyr Tyr Glu |     |
| 105 110 115   |     |
| gct gtt tgt ggc aca gat ggg aaa aca tat gac aac aga tgt gca ctg | 439 |
| Ala Val Cys Gly Thr Asp Gly Lys Thr Tyr Asp Asn Arg Cys Ala Leu |     |
| 120 125 130   |     |
| tgt gct gag aat gcg aaa acc ggg tcc caa att ggt gta aaa agt gaa | 487 |
| Cys Ala Glu Asn Ala Lys Thr Gly Ser Gln Ile Gly Val Lys Ser Glu |     |
| 135 140 145   |     |
| ggg gaa tgt aag agc agt aat cca gag cag gat gta tgc agt gct ttt | 535 |
| Gly Glu Cys Lys Ser Ser Asn Pro Glu Gln Asp Val Cys Ser Ala Phe |     |
| 150 155 160   |     |
| cgg ccc ttt gtt aga gat gga aga ctt gga tgc aca agg gaa aat gat | 583 |
| Arg Pro Phe Val Arg Asp Gly Arg Leu Gly Cys Thr Arg Glu Asn Asp |     |
| 165 170 175 180   |     |
| cct gtt ctt ggt cct gat ggg aag acg cat ggc aat aag tgt gca atg | 631 |
| Pro Val Leu Gly Pro Asp Gly Lys Thr His Gly Asn Lys Cys Ala Met |     |
| 185 190 195   |     |
| tgt gct gag ctg ttt tta aaa gaa gct gaa aat gcc aag cga gag ggt | 679 |
| Cys Ala Glu Leu Phe Leu Lys Glu Ala Glu Asn Ala Lys Arg Glu Gly |     |
| 200 205 210   |     |
| gaa act aga att cga cga aat gct gaa aag gat ttt tgc aag gaa tat | 727 |
| Glu Thr Arg Ile Arg Arg Asn Ala Glu Lys Asp Phe Cys Lys Glu Tyr |     |
| 215 220 225   |     |
| gaa aaa caa gtg aga aat gga agg ctt ttt tgt aca cgg gag agt gat | 775 |
| Glu Lys Gln Val Arg Asn Gly Arg Leu Phe Cys Thr Arg Glu Ser Asp |     |
| 230 235 240   |     |
| cca gtc cgt ggc cct gac ggc agg atg cat ggc aac aaa tgt gcc ctg | 823 |
| Pro Val Arg Gly Pro Asp Gly Arg Met His Gly Asn Lys Cys Ala Leu |     |
| 245 250 255 260   |     |
| tgt gct gaa att ttc aag cgg cgt ttt tca gag gaa aac agt aaa aca | 871 |
| Cys Ala Glu Ile Phe Lys Arg Arg Phe Ser Glu Glu Asn Ser Lys Thr |     |
| 265 270 275   |     |
| gat caa aat ttg gga aaa gct gaa gaa aaa act aaa gtt aaa aga gaa | 919 |
| Asp Gln Asn Leu Gly Lys Ala Glu Glu Lys Thr Lys Val Lys Arg Glu |     |
| 280 285 290   |     |

|                   |                   |                   |            |                   |                   |                   |                   |                   |                   |                   |                   |                   |            |                   |                   |      |
|-------------------|-------------------|-------------------|------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------|-------------------|-------------------|------|
| att<br>Ile        | gtg<br>Val        | aaa<br>Lys<br>295 | ctc<br>Leu | tgc<br>Cys        | agt<br>Ser        | caa<br>Gln        | tat<br>Tyr<br>300 | caa<br>Gln        | aat<br>Asn        | cag<br>Gln        | gca<br>Ala        | aag<br>Lys<br>305 | aat<br>Asn | gga<br>Gly        | ata<br>Ile        | 967  |
| ctt<br>Leu        | ttc<br>Phe<br>310 | tgt<br>Cys        | acc<br>Thr | aga<br>Arg        | gaa<br>Glu        | aat<br>Asn<br>315 | gac<br>Asp        | cct<br>Pro        | att<br>Ile        | cgt<br>Arg        | ggt<br>Gly<br>320 | cca<br>Pro        | gat<br>Asp | ggg<br>Gly        | aaa<br>Lys        | 1015 |
| atg<br>Met<br>325 | cat<br>His        | ggc<br>Gly        | aac<br>Asn | ttg<br>Leu        | tgt<br>Cys<br>330 | tcc<br>Ser        | atg<br>Met        | tgt<br>Cys        | caa<br>Gln        | gtc<br>Val<br>335 | tac<br>Tyr        | ttc<br>Phe        | caa<br>Gln | gca<br>Ala        | gaa<br>Glu<br>340 | 1063 |
| aat<br>Asn        | gaa<br>Glu        | gaa<br>Glu        | aag<br>Lys | aaa<br>Lys<br>345 | aag<br>Lys        | gct<br>Ala        | gaa<br>Glu        | gca<br>Ala        | cga<br>Arg<br>350 | gct<br>Ala        | aga<br>Arg        | aac<br>Asn        | aaa<br>Lys | aga<br>Arg<br>355 | gaa<br>Glu        | 1111 |
| tct<br>Ser        | gga<br>Gly        | aaa<br>Lys        | gca<br>Ala | acc<br>Thr        | tca<br>Ser        | tat<br>Tyr        | gca<br>Ala        | gag<br>Glu        | ctt<br>Leu        | tgc<br>Cys        | aat<br>Asn        | gaa<br>Glu        | tat<br>Tyr | cga<br>Arg        | aag<br>Lys        | 1159 |
| ctt<br>Leu        | gtg<br>Val        | agg<br>Arg        | aac<br>Asn | gga<br>Gly        | aaa<br>Lys        | ctt<br>Leu        | gct<br>Ala        | tgc<br>Cys        | acc<br>Thr        | aga<br>Arg        | gag<br>Glu        | aac<br>Asn        | gat<br>Asp | cct<br>Pro        | atc<br>Ile        | 1207 |
| cag<br>Gln        | ggc<br>Gly<br>390 | cca<br>Pro        | gat<br>Asp | ggg<br>Gly        | aaa<br>Lys        | gtg<br>Val<br>395 | cac<br>His        | ggc<br>Gly        | aac<br>Asn        | acc<br>Thr        | tgc<br>Cys        | tcc<br>Ser        | atg<br>Met | tgt<br>Cys        | gag<br>Glu        | 1255 |
| gtc<br>Val<br>405 | ttc<br>Phe        | ttc<br>Phe        | caa<br>Gln | gca<br>Ala        | gaa<br>Glu<br>410 | gaa<br>Glu        | gaa<br>Glu        | gaa<br>Glu        | aag<br>Lys        | aaa<br>Lys<br>415 | aag<br>Lys        | aag<br>Lys        | gaa<br>Glu | ggc<br>Gly        | gaa<br>Glu<br>420 | 1303 |
| tca<br>Ser        | aga<br>Arg        | aac<br>Asn        | aaa<br>Lys | aga<br>Arg        | caa<br>Gln        | tct<br>Ser        | aag<br>Lys        | agt<br>Ser        | aca<br>Thr        | gct<br>Ala        | tcc<br>Ser        | ttt<br>Phe        | gag<br>Glu | gag<br>Glu        | ttg<br>Leu        | 1351 |
| tgt<br>Cys        | agt<br>Ser        | gaa<br>Glu        | tac<br>Tyr | cgc<br>Arg        | aaa<br>Lys        | tcc<br>Ser        | agg<br>Arg        | aaa<br>Lys<br>445 | aac<br>Asn        | gga<br>Gly        | cgg<br>Arg        | ctt<br>Leu        | ttt<br>Phe | tgc<br>Cys        | acc<br>Thr        | 1399 |
| aga<br>Arg        | gag<br>Glu        | aat<br>Asn<br>455 | gac<br>Asp | ccc<br>Pro        | atc<br>Ile        | cag<br>Gln        | ggc<br>Gly<br>460 | cca<br>Pro        | gat<br>Asp        | ggg<br>Gly        | aaa<br>Lys        | atg<br>Met<br>465 | cat<br>His | ggc<br>Gly        | aac<br>Asn        | 1447 |
| acc<br>Thr        | tgc<br>Cys<br>470 | tcc<br>Ser        | atg<br>Met | tgt<br>Cys        | gag<br>Glu        | gcc<br>Ala<br>475 | ttc<br>Phe        | ttt<br>Phe        | caa<br>Gln        | caa<br>Gln        | gaa<br>Glu<br>480 | gaa<br>Glu        | aga<br>Arg | gca<br>Ala        | aga<br>Arg        | 1495 |
| gca<br>Ala<br>485 | aag<br>Lys        | gct<br>Ala        | aaa<br>Lys | aga<br>Arg        | gaa<br>Glu<br>490 | gct<br>Ala        | gca<br>Ala        | aag<br>Lys        | gaa<br>Glu        | atc<br>Ile<br>495 | tgc<br>Cys        | agt<br>Ser        | gaa<br>Glu | ttt<br>Phe        | cgg<br>Arg<br>500 | 1543 |
| gac<br>Asp        | caa<br>Gln        | gtg<br>Val        | agg<br>Arg | aat<br>Asn<br>505 | gga<br>Gly        | aca<br>Thr        | ctt<br>Leu        | ata<br>Ile        | tgc<br>Cys<br>510 | acc<br>Thr        | agg<br>Arg        | gag<br>Glu        | cat<br>His | aat<br>Asn<br>515 | cct<br>Pro        | 1591 |

|   |      |
|---|------|
| gtc cgt gga cca gat ggc aaa atg cat gga aac aag tgt gcc atg tgt | 1639 |
| Val Arg Gly Pro Asp Gly Lys Met His Gly Asn Lys Cys Ala Met Cys |      |
| 520 525 530   |      |
| gcc agt gtg ttc aaa ctt gaa gaa gaa gag aag aaa aat gat aaa gaa | 1687 |
| Ala Ser Val Phe Lys Leu Glu Glu Glu Glu Lys Lys Asn Asp Lys Glu |      |
| 535 540 545   |      |
| gaa aaa ggg aaa gtt gag gct gaa aaa gtt aag aga gaa gca gtt cag | 1735 |
| Glu Lys Gly Lys Val Glu Ala Glu Lys Val Lys Arg Glu Ala Val Gln |      |
| 550 555 560   |      |
| gag ctg tgc agt gaa tat cgt cat tat gtg agg aat gga cga ctc ccc | 1783 |
| Glu Leu Cys Ser Glu Tyr Arg His Tyr Val Arg Asn Gly Arg Leu Pro |      |
| 565 570 575 580   |      |
| tgt acc aga gag aat gat cct att gag ggt cta gat ggg aaa atc cac | 1831 |
| Cys Thr Arg Glu Asn Asp Pro Ile Glu Gly Leu Asp Gly Lys Ile His |      |
| 585 590 595   |      |
| ggc aac acc tgc tcc atg tgt gaa gcc ttc ttc cag caa gaa gca aaa | 1879 |
| Gly Asn Thr Cys Ser Met Cys Glu Ala Phe Phe Gln Gln Glu Ala Lys |      |
| 600 605 610   |      |
| gaa aaa gaa aga gct gaa ccc aga gca aaa gtc aaa aga gaa gct gaa | 1927 |
| Glu Lys Glu Arg Ala Glu Pro Arg Ala Lys Val Lys Arg Glu Ala Glu |      |
| 615 620 625   |      |
| aag gag aca tgc gat gaa ttt cgg aga ctt ttg caa aat gga aaa ctt | 1975 |
| Lys Glu Thr Cys Asp Glu Phe Arg Arg Leu Leu Gln Asn Gly Lys Leu |      |
| 630 635 640   |      |
| ttc tgc aca aga gaa aat gat cct gtg cgt ggc cca gat ggc aag acc | 2023 |
| Phe Cys Thr Arg Glu Asn Asp Pro Val Arg Gly Pro Asp Gly Lys Thr |      |
| 645 650 655 660   |      |
| cat ggc aac aag tgt gcc atg tgt aag gca gtc ttc cag aaa gaa aat | 2071 |
| His Gly Asn Lys Cys Ala Met Cys Lys Ala Val Phe Gln Lys Glu Asn |      |
| 665 670 675   |      |
| gag gaa aga aag agg aaa gaa gag gaa gat cag aga aat gct gca gga | 2119 |
| Glu Glu Arg Lys Arg Lys Glu Glu Glu Asp Gln Arg Asn Ala Ala Gly |      |
| 680 685 690   |      |
| cat ggt tcc agt ggt ggt gga gga gga aac act cag gac gaa tgt gct | 2167 |
| His Gly Ser Ser Gly Gly Gly Gly Gly Asn Thr Gln Asp Glu Cys Ala |      |
| 695 700 705   |      |
| gag tat cag gaa caa atg aaa aat gga aga ctc agc tgt act cgg gag | 2215 |
| Glu Tyr Gln Glu Gln Met Lys Asn Gly Arg Leu Ser Cys Thr Arg Glu |      |
| 710 715 720   |      |
| agt gat cct gta cgt gat gct gat ggc aaa tcg tac aac aat cag tgt | 2263 |
| Ser Asp Pro Val Arg Asp Ala Asp Gly Lys Ser Tyr Asn Asn Gln Cys |      |
| 725 730 735 740   |      |

|            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------|
| acc        | atg        | tgt        | aaa        | gca        | aaa        | ttg        | gaa        | aga        | gaa        | gca        | gag        | aga        | aaa        | aat        | gag        | 2311 |
| Thr        | Met        | Cys        | Lys        | Ala<br>745 | Lys        | Leu        | Glu        | Arg        | Glu<br>750 | Ala        | Glu        | Arg        | Lys        | Asn<br>755 | Glu        |      |
| tat        | tct        | cgc        | tcc        | aga        | tca        | aat        | ggg        | act        | gga        | tca        | gaa        | tca        | ggg        | aag        | gat        | 2359 |
| Tyr        | Ser        | Arg        | Ser<br>760 | Arg        | Ser        | Asn        | Gly        | Thr<br>765 | Gly        | Ser        | Glu        | Ser        | Gly<br>770 | Lys        | Asp        |      |
| aca        | tgt        | gat        | gag        | ttt        | aga        | agc        | caa        | atg        | aaa        | aat        | gga        | aaa        | ctt        | atc        | tgc        | 2407 |
| Thr        | Cys        | Asp<br>775 | Glu        | Phe        | Arg        | Ser        | Gln<br>780 | Met        | Lys        | Asn        | Gly        | Lys<br>785 | Leu        | Ile        | Cys        |      |
| act        | cga        | gaa        | agt        | gac        | cct        | gtc        | cgg        | ggg        | cca        | gat        | ggc        | aag        | aca        | cat        | ggg        | 2455 |
| Thr        | Arg<br>790 | Glu        | Ser        | Asp        | Pro        | Val<br>795 | Arg        | Gly        | Pro        | Asp        | Gly<br>800 | Lys        | Thr        | His        | Gly        |      |
| aat        | aag        | tgt        | act        | atg        | tgt        | aag        | gaa        | aaa        | ctg        | gaa        | agg        | gaa        | gca        | gct        | gaa        | 2503 |
| Asn<br>805 | Lys        | Cys        | Thr        | Met        | Cys<br>810 | Lys        | Glu        | Lys        | Leu        | Glu<br>815 | Arg        | Glu        | Ala        | Ala        | Glu<br>820 |      |
| aaa        | aaa        | aag        | aaa        | gag        | gat        | gaa        | gac        | agg        | agc        | aat        | aca        | gga        | gaa        | agg        | agc        | 2551 |
| Lys        | Lys        | Lys        | Lys<br>825 | Glu        | Asp        | Glu        | Asp        | Arg        | Ser<br>830 | Asn        | Thr        | Gly        | Glu        | Arg<br>835 | Ser        |      |
| aat        | aca        | gga        | gaa        | agg        | agc        | aat        | gac        | aaa        | gag        | gat        | ctg        | tgt        | cgt        | gaa        | ttt        | 2599 |
| Asn        | Thr        | Gly        | Glu<br>840 | Arg        | Ser        | Asn        | Asp        | Lys<br>845 | Glu        | Asp        | Leu        | Cys        | Arg<br>850 | Glu        | Phe        |      |
| cga        | agc        | atg        | cag        | aga        | aat        | gga        | aag        | ctt        | atc        | tgc        | acc        | aga        | gaa        | aat        | aac        | 2647 |
| Arg        | Ser        | Met<br>855 | Gln        | Arg        | Asn        | Gly        | Lys<br>860 | Leu        | Ile        | Cys        | Thr        | Arg<br>865 | Glu        | Asn        | Asn        |      |
| cct        | gtt        | cga        | ggc        | cca        | tat        | ggc        | aag        | atg        | cac        | atc        | aat        | aaa        | tgt        | gct        | atg        | 2695 |
| Pro        | Val<br>870 | Arg        | Gly        | Pro        | Tyr        | Gly<br>875 | Lys        | Met        | His        | Ile        | Asn<br>880 | Lys        | Cys        | Ala        | Met        |      |
| tgt        | cag        | agc        | atc        | ttt        | gat        | cga        | gaa        | gct        | aat        | gaa        | aga        | aaa        | aag        | aaa        | gat        | 2743 |
| Cys<br>885 | Gln        | Ser        | Ile        | Phe        | Asp<br>890 | Arg        | Glu        | Ala        | Asn        | Glu<br>895 | Arg        | Lys        | Lys        | Lys        | Asp<br>900 |      |
| gaa        | gag        | aaa        | tca        | agt        | agc        | aag        | ccc        | tca        | aat        | aat        | gca        | aag        | gat        | gag        | tgc        | 2791 |
| Glu        | Glu        | Lys        | Ser        | Ser<br>905 | Ser        | Lys        | Pro        | Ser        | Asn<br>910 | Asn        | Ala        | Lys        | Asp        | Glu        | Cys        |      |
| agt        | gaa        | ttt        | cga        | aac        | tat        | ata        | agg        | aac        | aat        | gaa        | ctc        | atc        | tgc        | cct        | aga        | 2839 |
| Ser        | Glu        | Phe<br>920 | Arg        | Asn        | Tyr        | Ile        | Arg        | Asn<br>925 | Asn        | Glu        | Leu        | Ile        | Cys<br>930 | Pro        | Arg        |      |
| gag        | aat        | gac        | cca        | gtg        | cac        | ggg        | gct        | gat        | gga        | aag        | ttc        | tat        | aca        | aac        | aag        | 2887 |
| Glu        | Asn        | Asp<br>935 | Pro        | Val        | His        | Gly        | Ala<br>940 | Asp        | Gly        | Lys        | Phe        | Tyr<br>945 | Thr        | Asn        | Lys        |      |
| tgc        | tac        | atg        | tgc        | aga        | gct        | gtc        | ttt        | cta        | aca        | gaa        | gct        | ttg        | gaa        | agg        | gca        | 2935 |
| Cys        | Tyr<br>950 | Met        | Cys        | Arg        | Ala        | Val<br>955 | Phe        | Leu        | Thr        | Glu        | Ala<br>960 | Leu        | Glu        | Arg        | Ala        |      |



[illegible]

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<211> 105
<212> DNA
<213> mammalian
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gttcttggtc ctgatgggaa gacgcatggc aataagtgtg caatg 105
```

```
<210> 9
<211> 105
<212> DNA
<213> mammalian
```

```
<400> 9
aatgaatatc gaaagcttgt gaggaacgga aaacttgctt gcaccagaga gaacgatcct 60
atccagggcc cagatgggaa agtgcacggc aacacctgct ccatg                               105
```

```
<210> 10
<211> 99
<212> DNA
<213> mammalian
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```
<400> 10
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gttcgaggcc catatggcaa gatgcacatc aataaatgt 99
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<210> 11
<211> 105
<212> DNA
<213> mammalian
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gtgcacggtg ctgatggaaa gttctataca aacaagtgct acatg                               105
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<211> 156
<212> DNA
<213> mammalian
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tgtgggtgacg atggccaaac ctacaacaat ccttgcacgc tctgtcatga aaacctgata 120
cgccaaacaa atacacacat ccgcagtaca gggaag                               156
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531 Rec'd PC.

26 DEC 2001

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<211> 1064  
 <212> PRT  
 <213> Mamalia

&lt;400&gt; 1

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Lys | Ile | Ala | Thr | Val | Ser | Val | Leu | Leu | Pro | Leu | Ala | Leu | Cys | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Ile | Gln | Asp | Ala | Ala | Ser | Lys | Asn | Glu | Asp | Gln | Glu | Met | Cys | His | Glu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Phe | Gln | Ala | Phe | Met | Lys | Asn | Gly | Lys | Leu | Phe | Cys | Pro | Gln | Asp | Lys |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Lys | Phe | Phe | Gln | Ser | Leu | Asp | Gly | Ile | Met | Phe | Ile | Asn | Lys | Cys | Ala |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Thr | Cys | Lys | Met | Ile | Leu | Glu | Lys | Glu | Ala | Lys | Ser | Gln | Lys | Arg | Ala |
|     | 65  |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Arg | His | Leu | Ala | Arg | Ala | Pro | Lys | Ala | Thr | Ala | Pro | Thr | Glu | Leu | Asn |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Cys | Asp | Asp | Phe | Lys | Lys | Gly | Glu | Arg | Asp | Gly | Asp | Phe | Ile | Cys | Pro |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Asp | Tyr | Tyr | Glu | Ala | Val | Cys | Gly | Thr | Asp | Gly | Lys | Thr | Tyr | Asp | Asn |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Arg | Cys | Ala | Leu | Cys | Ala | Glu | Asn | Ala | Lys | Thr | Gly | Ser | Gln | Ile | Gly |
|     |     | 130 |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Val | Lys | Ser | Glu | Gly | Glu | Cys | Lys | Ser | Ser | Asn | Pro | Glu | Gln | Asp | Val |
|     | 145 |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Cys | Ser | Ala | Phe | Arg | Pro | Phe | Val | Arg | Asp | Gly | Arg | Leu | Gly | Cys | Thr |
|     |     |     |     | 165 |     |     |     | 170 |     |     |     |     |     | 175 |     |
| Arg | Glu | Asn | Asp | Pro | Val | Leu | Gly | Pro | Asp | Gly | Lys | Thr | His | Gly | Asn |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Lys | Cys | Ala | Met | Cys | Ala | Glu | Leu | Phe | Leu | Lys | Glu | Ala | Glu | Asn | Ala |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Lys | Arg | Glu | Gly | Glu | Thr | Arg | Ile | Arg | Arg | Asn | Ala | Glu | Lys | Asp | Phe |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Cys | Lys | Glu | Tyr | Glu | Lys | Gln | Val | Arg | Asn | Gly | Arg | Leu | Phe | Cys | Thr |
|     | 225 |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Arg | Glu | Ser | Asp | Pro | Val | Arg | Gly | Pro | Asp | Gly | Arg | Met | His | Gly | Asn |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Lys | Cys | Ala | Leu | Cys | Ala | Glu | Ile | Phe | Lys | Arg | Arg | Phe | Ser | Glu | Glu |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Asn | Ser | Lys | Thr | Asp | Gln | Asn | Leu | Gly | Lys | Ala | Glu | Glu | Lys | Thr | Lys |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Val | Lys | Arg | Glu | Ile | Val | Lys | Leu | Cys | Ser | Gln | Tyr | Gln | Asn | Gln | Ala |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Lys | Asn | Gly | Ile | Leu | Phe | Cys | Thr | Arg | Glu | Asn | Asp | Pro | Ile | Arg | Gly |
|     | 305 |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |

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Pro Asp Gly Lys Met His Gly Asn Leu Cys Ser Met Cys Gln Val Tyr  
325 330 335

Phe Gln Ala Glu Asn Glu Glu Lys Lys Lys Ala Glu Ala Arg Ala Arg  
340 345 350

Asn Lys Arg Glu Ser Gly Lys Ala Thr Ser Tyr Ala Glu Leu Cys Asn  
355 360 365

Glu Tyr Arg Lys Leu Val Arg Asn Gly Lys Leu Ala Cys Thr Arg Glu  
370 375 380

Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys Val His Gly Asn Thr Cys  
385 390 395 400

Ser Met Cys Glu Val Phe Phe Gln Ala Glu Glu Glu Glu Lys Lys Lys  
405 410 415

Lys Glu Gly Glu Ser Arg Asn Lys Arg Gln Ser Lys Ser Thr Ala Ser  
420 425 430

Phe Glu Glu Leu Cys Ser Glu Tyr Arg Lys Ser Arg Lys Asn Gly Arg  
435 440 445

Leu Phe Cys Thr Arg Glu Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys  
450 455 460

Met His Gly Asn Thr Cys Ser Met Cys Glu Ala Phe Phe Gln Gln Glu  
465 470 475 480

Glu Arg Ala Arg Ala Lys Ala Lys Arg Glu Ala Ala Lys Glu Ile Cys  
485 490 495

Ser Glu Phe Arg Asp Gln Val Arg Asn Gly Thr Leu Ile Cys Thr Arg  
500 505 510

Glu His Asn Pro Val Arg Gly Pro Asp Gly Lys Met His Gly Asn Lys  
515 520 525

Cys Ala Met Cys Ala Ser Val Phe Lys Leu Glu Glu Glu Glu Lys Lys  
530 535 540

Asn Asp Lys Glu Glu Lys Gly Lys Val Glu Ala Glu Lys Val Lys Arg  
545 550 555 560

Glu Ala Val Gln Glu Leu Cys Ser Glu Tyr Arg His Tyr Val Arg Asn  
565 570 575

Gly Arg Leu Pro Cys Thr Arg Glu Asn Asp Pro Ile Glu Gly Leu Asp  
580 585 590

Gly Lys Ile His Gly Asn Thr Cys Ser Met Cys Glu Ala Phe Phe Gln  
595 600 605

Gln Glu Ala Lys Glu Lys Glu Arg Ala Glu Pro Arg Ala Lys Val Lys  
610 615 620

Arg Glu Ala Glu Lys Glu Thr Cys Asp Glu Phe Arg Arg Leu Leu Gln  
625 630 635 640

Asn Gly Lys Leu Phe Cys Thr Arg Glu Asn Asp Pro Val Arg Gly Pro  
645 650 655

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|            |            |            |            |            |            |            |             |            |            |            |            |             |            |            |            |
|------------|------------|------------|------------|------------|------------|------------|-------------|------------|------------|------------|------------|-------------|------------|------------|------------|
| Asp        | Gly        | Lys        | Thr<br>660 | His        | Gly        | Asn        | Lys         | Cys<br>665 | Ala        | Met        | Cys        | Lys         | Ala<br>670 | Val        | Phe        |
| Gln        | Lys        | Glu<br>675 | Asn        | Glu        | Glu        | Arg        | Lys<br>680  | Arg        | Lys        | Glu        | Glu        | Glu<br>685  | Asp        | Gln        | Arg        |
| Asn        | Ala<br>690 | Ala        | Gly        | His        | Gly        | Ser<br>695 | Ser         | Gly        | Gly        | Gly        | Gly        | Gly         | Asn        | Thr        | Gln        |
| Asp<br>705 | Glu        | Cys        | Ala        | Glu        | Tyr<br>710 | Gln        | Glu         | Gln        | Met        | Lys<br>715 | Asn        | Gly         | Arg        | Leu        | Ser<br>720 |
| Cys        | Thr        | Arg        | Glu        | Ser<br>725 | Asp        | Pro        | Val         | Arg        | Asp<br>730 | Ala        | Asp        | Gly         | Lys        | Ser<br>735 | Tyr        |
| Asn        | Asn        | Gln        | Cys<br>740 | Thr        | Met        | Cys        | Lys         | Ala<br>745 | Lys        | Leu        | Glu        | Arg         | Glu<br>750 | Ala        | Glu        |
| Arg        | Lys        | Asn<br>755 | Glu        | Tyr        | Ser        | Arg        | Ser<br>760  | Arg        | Ser        | Asn        | Gly        | Thr<br>765  | Gly        | Ser        | Glu        |
| Ser        | Gly<br>770 | Lys        | Asp        | Thr        | Cys        | Asp<br>775 | Glu         | Phe        | Arg        | Ser        | Gln<br>780 | Met         | Lys        | Asn        | Gly        |
| Lys<br>785 | Leu        | Ile        | Cys        | Thr        | Arg<br>790 | Glu        | Ser         | Asp        | Pro        | Val<br>795 | Arg        | Gly         | Pro        | Asp        | Gly<br>800 |
| Lys        | Thr        | His        | Gly        | Asn<br>805 | Lys        | Cys        | Thr         | Met        | Cys<br>810 | Lys        | Glu        | Lys         | Leu        | Glu<br>815 | Arg        |
| Glu        | Ala        | Ala        | Glu<br>820 | Lys        | Lys        | Lys        | Lys         | Glu<br>825 | Asp        | Glu        | Asp        | Arg         | Ser<br>830 | Asn        | Thr        |
| Gly        | Glu        | Arg<br>835 | Ser        | Asn        | Thr        | Gly        | Glu<br>840  | Arg        | Ser        | Asn        | Asp        | Lys<br>845  | Glu        | Asp        | Leu        |
| Cys        | Arg<br>850 | Glu        | Phe        | Arg        | Ser        | Met<br>855 | Gln         | Arg        | Asn        | Gly        | Lys<br>860 | Leu         | Ile        | Cys        | Thr        |
| Arg<br>865 | Glu        | Asn        | Asn        | Pro        | Val<br>870 | Arg        | Gly         | Pro        | Tyr        | Gly<br>875 | Lys        | Met         | His        | Ile        | Asn<br>880 |
| Lys        | Cys        | Ala        | Met        | Cys<br>885 | Gln        | Ser        | Ile         | Phe        | Asp<br>890 | Arg        | Glu        | Ala         | Asn        | Glu<br>895 | Arg        |
| Lys        | Lys        | Lys        | Asp<br>900 | Glu        | Glu        | Lys        | Ser         | Ser<br>905 | Ser        | Lys        | Pro        | Ser         | Asn<br>910 | Asn        | Ala        |
| Lys        | Asp        | Glu<br>915 | Cys        | Ser        | Glu        | Phe        | Arg<br>920  | Asn        | Tyr        | Ile        | Arg        | Asn<br>925  | Asn        | Glu        | Leu        |
| Ile        | Cys<br>930 | Pro        | Arg        | Glu        | Asn        | Asp<br>935 | Pro         | Val        | His        | Gly        | Ala<br>940 | Asp         | Gly        | Lys        | Phe        |
| Tyr<br>945 | Thr        | Asn        | Lys        | Cys        | Tyr<br>950 | Met        | Cys         | Arg        | Ala        | Val<br>955 | Phe        | Leu         | Thr        | Glu        | Ala<br>960 |
| Leu        | Glu        | Arg        | Ala        | Lys<br>965 | Leu        | Gln        | Glu         | Lys        | Pro<br>970 | Ser        | His        | Val         | Arg        | Ala<br>975 | Ser        |
| Gln        | Glu        | Glu        | Asp<br>980 | Ser        | Pro        | Asp        | Ser         | Phe<br>985 | Ser        | Ser        | Leu        | Asp         | Ser<br>990 | Glu        | Met        |
| Cys        | Lys        | Asp<br>995 | Tyr        | Arg        | Val        | Leu        | Pro<br>1000 | Arg        | Ile        | Gly        | Tyr        | Leu<br>1005 | Cys        | Pro        | Lys        |

Cys Ala Met

35

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<210> 5
<211> 35
<212> PRT
<213> Mamalia
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Ser Glu Phe Arg Asn Tyr Ile Arg Asn Asn Glu Leu Ile Cys Pro Arg  
1 5 10 15  
Glu Asn Asp Pro Val His Gly Ala Asp Gly Lys Phe Tyr Thr Asn Lys  
20 25 30  
Cys Tyr Met  
35

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<211> 52
<212> PRT
<213> Mamalia
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Leu Lys Pro Val Cys Gly Asp Asp Gly Gln Thr Tyr Asn Asn Pro Cys
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Met Leu Cys His Glu Asn Leu Ile Arg Gln Thr Asn Thr His Ile Arg
      35          40          45

Ser Thr Gly Lys
      50

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<210> 7
<211> 3528
<212> DNA
<213> Mamalia
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| gtcagtgctt | ctgccctttgg | ctcttttgct  | catacaagat | gctgccagta | agaatgaaga | 120 |  |
| tcaggaaatg | tgccatgaat  | ttcaggcatt  | tatgaaaaat | ggaaaactgt | tctgtcccca | 180 |  |
| ggataagaaa | ttttttcaaa  | gtcttgatgg  | aataatgttc | atcaataaat | gtgccacgtg | 240 |  |
| caaaatgata | ctggaaaaaag | aagcaaaatc  | acagaagagg | gccaggcatt | tagcaagagc | 300 |  |
| tccaaggct  | actgccccaa  | cagagctgaa  | ttgtgatgat | tttaaaaaag | gagaaagaga | 360 |  |
| tggggatttt | atctgtcctg  | attattatga  | agctgtttgt | ggcacagatg | ggaaaacata | 420 |  |
| tgacaacaga | tgtgcactgt  | gtgtgtgaaa  | tgcgaaaacc | gggtcccaaa | ttggtgtaaa | 480 |  |
| aagtgaaggg | gaatgtaaga  | gcagtaatcc  | agagcaggat | gtatgcagtg | cttttcggcc | 540 |  |
| ctttgttaga | gatggaagac  | ttggatgcac  | aaggggaaat | gatcctgttc | ttggtcctga | 600 |  |
| tgggaagacg | catggcaata  | agtgtgcaat  | gtgtgctgag | ctgtttttta | aagaagctga | 660 |  |
| aaatgccaa  | cgagagggtg  | aaactagaat  | tcgacgaat  | gctgaaaag  | atttttgcaa | 720 |  |
| ggaatatgaa | aaacaagtga  | gaaatggaag  | gcttttttgt | acacgggaga | gtgatccagt | 780 |  |
| ccgtggccct | gacggcagga  | tgcatggcaa  | caaatgtgcc | ctgtgtgctg | aaattttcaa | 840 |  |
| gcggcgtttt | tcagaggaaa  | acagtaaaac  | agatcaaaat | ttgggaaaag | ctgaagaaaa | 900 |  |

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```

aactaaagtt aaaagagaaa ttgtgaaact ctgcagtc aa tatcaaaatc aggcaaagaa 960
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 <211> 105  
 <212> DNA  
 <213> Mamalia

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<210> 9  
 <211> 105  
 <212> DNA  
 <213> Mamalia

<400> 9



- 7 -

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<210> 10  
<211> 99  
<212> DNA  
<213> Mamalia

<400> 10  
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<211> 105  
<212> DNA  
<213> Mamalia

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<210> 12  
<211> 156  
<212> DNA  
<213> Mamalia

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cgccaaacaa atacacacat ccgcagtaca ggaag 156